REMARKS

The presently claimed invention concerns a method for biasing the amplification of the DNA molecules in a sample such that a nucleic acid molecule having a specific nucleotide at a selected position (e.g., a polymorphic site) is preferentially amplified relative to an otherwise identical nucleic acid molecule not having the specific nucleotide at the selected position. The method is useful for preferentially amplifying at least a portion of one allele of a gene relative to another, different allele of the gene in a sample containing both alleles of the gene as well as for other purposes.

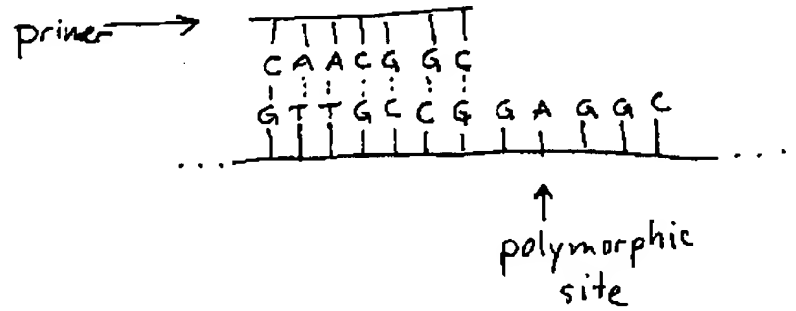
Rejections Under 35 U.S.C. §103

The Examiner rejected claims 10-16 as allegedly obvious in view of Tyagi et al. (U.S. Patent No. 6,277,607) in view of Newton et al. (U.S. Patent No. 5,595,890). According to the Examiner, Tygai et al. teaches all of the elements of the present claims except "primers that do not hybridize to a polymorphic site" Also according to the Examiner, Newton et al. teaches primers having a mismatch at a polymorphic site. Also according to the Examiner, one skilled in the art would have been motivated to modify the method of Tygai et al. by using primers with a mismatch at the polymorphic site as taught by Newton et al. resulting in the presently claimed invention.

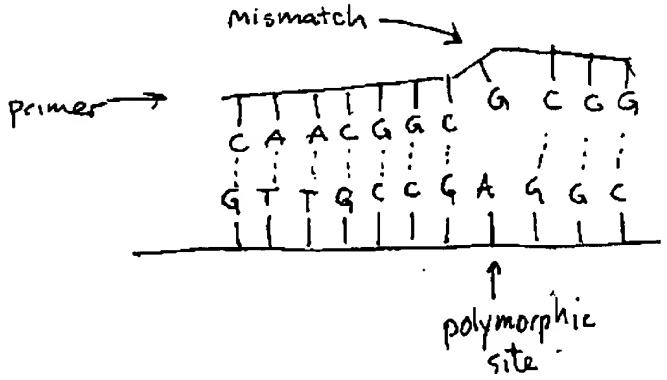
Applicants disagree with the Examiner's characterization of the present claims and the Examiner's conclusion that the claims are obvious in view of Tyagi et al. and Newton et al.

The Examiner is seemingly of the view that the present claims entail the use of primers that have a mismatch at a polymorphic site. It appears that the Examiner has misunderstood the present claims. The present claims entail the use of a first primer and a second primer which "flank the polymorphic site such that neither the first primer nor the second primer hybridizes to the polymorphic site". As explained previously, the term "flank" means that one primer lies to one side of the polymorphic site (e.g., the upstream side) and the other primer lies to the other side of the polymorphic site (e.g., the downstream side). This much is clear from the commonly understood meaning of the term "flank." For example, Webster's Ninth New Collegiate

Dictionary (Merriam-Webster Inc., Springfield, MA (1983) provides the following definition of "flank": "to be situated to the side of; esp: to be situated on both sides of."
The difference between a primer that flanks a polymorphic site and one which simply has a mismatch at the polymorphic site can be depicted. The sketch below depicts a primer that that flanks a polymorphic site.



This differs greatly from a primer which simply has a mismatch at the polymorphic site. The sketch below depicts a primer having a mismatch a polymorphic site.



Thus, it can be clearly seen that the primers of the present claims differ from primers that have a mismatch at the polymorphic site because the primers of the present claims hybridize to the template to one side or the other of the polymorphic site. Thus, one primer hybridizes upstream of the polymorphic site and the other primer hybridizes downstream of the polymorphic site.

Of course, the present claims also specify that the primers do not hybridize to the polymorphic site. This is inevitably true since the primers are located to either side of the polymorphic site.

The meaning of the term "flank" is also clear from the description of the arrangement of the primers as described on page 8 of the specification.

> Methods described in the present invention first use amplification (preferably PCR amplification) using amplification oligonucleotides (primers) flanking a polymorphic site. The 3' end of one of the primers is close, highly preferably within 16 nucleotides, of a polymorphic site in template DNA. The second primer may lie at any distance from the first primer on the opposite side of the polymorphic site providing effective amplification.

Moreover, Figs. 14 and 15 which clearly show a primer that is to one side of a polymorphic site, i.e., flanking a polymorphic site. Thus, contrary to the Examiner's understanding, in the claimed methods, neither primer extends over the polymorphic site. Instead the primers are located on either side of the polymorphic site.

Neither Tyagi et al. nor Newton et al. teaches or suggests primers that flank a polymorphic site. Tyagi et al. has been discussed previously. Newton et al. describes primers which can include a mismatch at the polymorphic site (see, e.g., col. 11, lines 35-50) and can also have mismatches to the template at other positions (see col. 12, lines 15-26, as noted by the Examiner). However, Newton et al. never suggests the use of primers which flank a polymorphic site. Indeed, such primers would not be useful in the method described by Newton et al. As described in Newton et al. at lines 47-59 of column 12, the disclosed method depends on the use of a diagnostic primer having a terminal nucleotide that is complementary to, i.e., is a match for either the variant nucleotide or the normal nucleotide at the polymorphic site. Primer that flanked the polymorphic site would be utterly useless in the method described in Newton et al. because it would not include a nucleotide complementary to either the variant nucleotide at the polymorphic site or the normal nucleotide at the polymorphic site.

Nothing in either Tyagi et al. or Newton et al. can be seen as teaching or suggesting the use of a pair of primers that flank a polymorphic site. Thus, the cited references, no matter how combined cannot render the present claims obvious. Applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn and the pending claims be allowed.

Enclosed is a Petition for Extension of Time with the appropriate fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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